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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/549,463	04/14/2000	Guus Hatteboer	4038.1US	8657

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EXAMINER	
MITRA, RITA	
ART UNIT	PAPER NUMBER
1653	

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Please find below and/or attached an Office communication concerning this application or proceeding.

File Copy

Office Action Summary	Application No.	Applicant(s)	
	09/549,463	HATTEBOER ET AL.	
	Examiner	Art Unit	
	Rita Mitra	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 February 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,5-7,11,13,14,73-86 and 96-105* is/are pending in the application.

4a) Of the above claim(s) *103 and 104* is/are withdrawn from consideration.

5)☒ Claim(s) *98 and 100-102* is/are allowed.

6)☒ Claim(s) *1, 3, 5-7, 11, 13, 14, 73-86, 96, 97, 99 and 105* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☐ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4)☐ Interview Summary (PTO-413) Paper No(s). _____.
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

DETAILED ACTION

Status of the Claims

Applicants' amendment and response to office action dated November 20, 2002, filed on February 6, 2003 in paper #18 is acknowledged. Claims 1, 6, 7, 11, 73, 81-86 and 96 have been amended and entered, it should be noted that in claims 82-86 only Influenza virus is examined for the selection of viral protein as stated in previous office action (paper #16).

Newly submitted claims 103 and 104 directed to an invention that is independent or distinct from the invention originally claimed for the following reasons:

New claims 97-105 have been added, however, claims 103 and 104 are not entered and considered for examination because the original elected claims encompass E1A protein only, and not E1B protein. E1B protein is a different protein requires additional and different searches from that of E1A. The search of one would not have been a complete search of patent and non-patent technical literature.

Since applicants have received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 103 and 104 withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Therefore, claims 1, 3, 5-7, 11, 13, 14, 73-86, 96-102 and 105 are currently pending to which the following grounds for rejection are or remain applicable.

Response to Remarks and Arguments

Withdrawal of Objection/ Rejection

Objection to claims as to numbering is withdrawn.

Rejection under 35 U.S.C. 112, first paragraph

The rejection of claims 1, 3, 5, 6, 7, 11, 13, 14, 73-75, 76 and 96 under **35 U.S.C. 112, first paragraph**, is withdrawn in view of applicants' amendment to claims 1, 6, 7 and 96.

Rejection under 35 U.S.C. 112, second paragraph

The rejection of claims 1, 3, 5, 7, 11, 13, 14, 73 and 76-86 under **35 U.S.C. 112, second paragraph**, is withdrawn in view of applicants' amendment to claim 1.

Rejections unde 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 77-86 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 77-86 direct to a method of claims 1 and 6, wherein the proteinaceous substance comprises a viral protein other than an adenoviral protein. The viral protein selected for the current prosecution is an influenza virus neuramidase or a hemagglutinin. Specification at page 19, lines 11-13 indicates that Applicants have now found that cells which include adenoviral E1 sequences, preferably in their genome are capable of producing the viral protein in significant amounts. However, specification fails to provide a description or a demonstration in support of this statement. Although the specification outlines art-recognized procedures for producing viral protein using adenoviral E1A variants page 21, this is not adequate guidance as to the nature of functional derivatives that may be constructed. Thus, further experimentation is required to make and use the claimed invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 and dependent claims 77-86 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for producing a proteinaceous substance in a eukaryotic cell comprising providing a eukaryotic cell having a nucleic acid sequence that encodes one adenoviral E1A protein and with a gene encoding a recombinant proteinaceous substance; does not reasonably provide enablement for a method, wherein the proteinaceous substance comprises a viral protein other than an adenoviral protein. The specification does not enable a person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

There are no indicia that the present application enables the full scope in view of the structure corresponding to a viral protein other than an adenoviral protein as discussed in the following stated rejection. The present application provides no indicia and no teaching/guidance as to how the full scope of the claims is encompassed.

In this regard, the application disclosure and claims have been compared per the factors indicated in the decision *In re Wands*, 8 USPQ2d 1400 (Fed. Cir., 1988) as to undue experimentation. The factors include: 1) the nature of the invention; 2) the breadth of the claims 3) the amount of direction or guidance presented; 4) the presence or absence of working examples; 5) the quantity of experimentation necessary; 5); 6) the predictability or unpredictability of the art; 7) the state of the prior art; and, 8) the relative skill of those skilled in the art;

Each factor is addressed below on the basis of comparison of the disclosure, the claims and the state of the prior art in the assessment of undue experimentation.

1) the nature of the invention:

The nature of the invention is defined by the claims, which include a process for the production of a proteinaceous substance in eukaryotic cell using a gene construct, having nucleic acid sequence that encodes one adenoviral E1A protein and with a gene encoding a recombinant proteinaceous substance. Claims 1 and the dependent claims 77-86 thereto are directed to a process for the production of a proteinaceous substance in eukaryotic cell using a gene construct, having nucleic acid sequence that encodes one adenoviral E1 protein (claim 1) or a viral protein other than adenoviral protein (claims 77-86) and with a gene encoding a recombinant proteinaceous substance. The specification, however, only discloses cursory conclusions (see page 19), without data to support the findings, which state that the invention provides a method for enhancing production of a recombinant proteinaceous substance in a eukaryotic cell, including providing the eukaryotic cell with a nucleic acid encoding at least part of the proteinaceous substance, wherein the coding sequence is under control of a CMV-promoter, an E1A promoter or a functional homologue, derivative and/or fragment of either and further providing the cell with E1A activity or E1A-like activity. However, specification does not provide a description of that proteinaceous substance that comprises a viral protein other than an adenoviral protein.

2) the breadth of the claims:

The breadth of the claims is broad and encompasses an unspecified number of variants regarding a viral protein other than adenovirus E1A protein, which are not specifically described or demonstrated in the specification. Claims 77-86 are directed to a method of claim 1, wherein the proteinaceous substance comprises a viral protein other than an adenoviral protein. The viral protein selected for the current prosecution is an influenza virus neuramidase and/or a hemagglutinin. Specification at page 19, lines 11-13 indicates that Applicants have now found that cells which include adenoviral E1 sequences, preferably in their genome are capable of producing the viral protein in significant amounts. However, specification fails to provide a description or a demonstration in support of this statement. Although the specification outlines art-recognized procedures for producing viral protein using adenoviral E1A variants, this is not

adequate guidance as to the nature of functional derivatives that may be constructed. Thus, further experimentation is required to make and use the claimed invention.

As for factors 3-5:

3) the amount of direction or guidance presented;

4) the presence or absence of working examples; and

5) the quantity of experimentation necessary:

No description or Examples are provided for the enablement of claimed variants. The experimentation involved to enable the invention may constitute routine experimentation, however, because of the limited information in the specification it would require undue and excessive experimentation. No specific description is provided about the structure of influenza viral protein neither any activity of those proteins have been demonstrated. Without more guidance from the specification it would require undue and excessive experimentation for a person having skill in the art to be able to make and use the claimed invention.

6) the predictability or unpredictability of the art:

The invention is highly unpredictable for the reasons set forth for factors 1-5.

As for factors 7 and 8:

7) the state of the prior art

8) the relative skill of those skilled in the art:

The prior art has shown that the (Setoguchi et al. Blood, vol. 84 (9), pp2946-2953, November 1, 1994) a recombinant adenovirus AdMLP.Epo construct having human Epo gene when introduced into human hepatocyte cell line Hep3B resulted in a 15-fold increase in Epo production in 24 hours (see section below of 102(b) rejection), however, the general knowledge and level of the skill in the art do not supplement the omitted description, the specification needs to provide specific guidance on the structure and function for the influenza viral protein.

In consideration of each of factors 1-8, it is apparent that there is undue experimentation because in summary, the scope of the claim is broad, the working example does not demonstrate the claimed variants, the guidance/the teaching in the specification is limited, and the outcome is unpredictable for the various modified forms, it is necessary to have additional guidance and to carry out further experimentation to assess the property of the variants. Therefore, due to large quantity of experimentation necessary to determine an activity or property of the disclosed process using influenza viral protein and the variants thereof, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of modification on influenza viral protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and /or use the claimed invention in its full scope.

Rejection under 35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3, 5, 6, 7, 11, 13, 14, 73, 74, 75, 76 and 96 are/remain rejected under 35 U.S.C. 102(b) as being anticipated by Setoguchi et al. (Blood, vol. 84 (9), pp2946-2953, November 1, 1994). Setoguchi et al. teach a recombinant adenovirus AdMLP.Epo construct by deleting the majority of E1 from adenovirus type 5, and replacing E1 with an expression cassette containing the adenovirus type 5 major late promoter (MLP) and the human Epo gene (see Abstract). Setoguchi et al. further demonstrated infection of human hepatocyte cell line Hep3B with AdMLP.Epo that resulted in a 15-fold increase in Epo production in 24 hours (see Abstract, Materials and Methods at page 2946, col 2, page 2947, col 1 and 2; and Fig 1 and Fig 2), thus

anticipating claims 1, 3, 5, 6, 7, 11, 13, 14, 73, 74, 75, 76 and 96 of instant application. Setoguchi et al.'s recombinant molecule in cultured human hepatoma cell line Hep3B (ATCC HB8064) is considered for the eukaryotic cell of claims 1 and 6 because the claim requires a eukaryotic cell (human cell in claim 6) having a nucleic acid sequence encoding at least one adenoviral E1 protein, a gene encoding a recombinant proteinaceous substance (a human recombinant protein in claim 6), culturing said cell in a suitable medium and harvesting at least one proteinaceous substance (human recombinant protein in claim 6 and a protein in claim 105) from said cell. Further Setoguchi's eukaryotic cell is considered for the mammalian cell of claim 3 and for the human cell of claim 76, wherein the human Epo gene of Setoguchi is considered for the gene encoding a proteinaceous substance of claims 5, 11 and 73 and erythropoietin of claims 13, 14 and 74, 75 of the instant application. Setoguchi's hepatoma cell line is considered for an eukaryotic cell derived from a primary cell (claim 97), and a human cell derived from a primary cell in claim 99.

Applicants' arguments at page 10-11 are fully considered but not found persuasive. Applicants indicate that Setoguchi et al. does not teach each every element of the pending claims, the construct (AdMLP.Epo) of Setoguchi has the majority of E1 deleted and the genomes of the cells into which the construct is transferred for the production of Epo do not include sequences encoding at least one adenoviral E1 protein. This is not persuasive because Setoguchi's construct AdMLP.Epo contains the essential part of the adenovirus E1 protein in the expression cassette, for example the adenovirus type 5 (Ad5)major late promoter (MLP) and the Epo gene with the plasmid containing the Ad5 genome and . Therefore, this construct is considered for the full length E1 protein of claims 1 and 6 of instant application for the production of Epo (a proteinaceous substance of claims 5, 11, 73 and erythropoietin of claims 13, 14 and 74, 75 of the instant application), therefore, claims 1, 3, 5-7, 11, 13, 14, 73-76, 96, 97, 99 and 105 of the instant application are being anticipated by Setoguchi et al.

Conclusion

Claims 1, 3, 5-7, 11, 13, 14, 73-86, 96, 97, 99 and 105 are rejected.

Claims 98, 100-102 are allowable because they are free of art.

Inquiries

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Rita Mitra whose telephone number is (703) 605-1211. The Examiner can normally be reached from 9:30 a.m. to 6:30 p.m. on weekdays. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Dr. Christopher Low, can be reached at (703) 308-2923. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Fax Center number is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Rita Mitra, Ph.D.

May 15, 2003

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